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(54) Title: SYNERGISTIC COMPOSITIONS FOR HAIR RESTORATION CONTAINING DIMETHYLSULFONE AND A SULPHYDRYL GROUP RELEASING AGENT

(57) Abstract

The present invention relates to synergistic compositions comprising methylsulphonylmethane and a physiologically acceptable, organic, in vivo sulphydryl group releasing agent and their use in formulations and methods of treatment for at least one of arresting hair loss and stimulating hair growth.

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SYNERGISTIC COMPOSITIONS FOR HAIR RESTORATION CONTAINING DIMETHYLSULFONE AND A SULPHYDRYL GROUP RELEASING AGENT

The present invention relates to synergistic compositions suitable for use in hair restoration.

Excessive hair loss and premature baldness continue to be a subject of major interest not only because of the therapeutic challenge, but also because of the high level of anxiety inflicted by this disorder and its social implications. While many products have been introduced to combat this problem, none have been directed at the aetiopathological processes responsible for the hair loss. Thus they all have limited efficacy or a short lasting effect which does little if anything to reverse the disorder. It is, consequently, an object of this invention to avoid or minimise one or more of these disadvantages.

The present invention provides a synergistic composition for use in improving the scalp condition comprising methyl sulphonylmethane (MSM) and a physiologically acceptable, organic, in vivo sulphydryl-group releasing agent.

It has unexpectedly been found that the addition of a sulphydryl-containing agent to MSM augments the therapeutic advantages of this agent in arresting hair loss and stimulating its growth, in a synergistic manner, that is, the sum of the individual actions of the ingredients is less than that of their combination together. It has also been found that the composition has the advantageous property of adherence to the skin thereby affording prolonged contact with the treatment area and an enhanced therapeutic delivery. In vivo and in vitro experiments are indicative of the compositions of the present invention exhibiting the following actions:-

1. Scavenging of oxygen-derived free radicals which are cytotoxic agents implicated in tissue damage and injury besides impairing the process of healing and repair.

2. Cytoprotection which refers to sustaining the physio-chemical properties of biological tissues, thus increasing their resistance to noxious stimuli.

3. Biosynthesis and donation of sulphur which effect enhanced repair and healing.

While not limiting the scope of this invention, it is believed that one or more of these actions is to a greater or lesser extent responsible for the beneficial effects provided by the compositions of the present invention.

Preferred sulphyldryl group releasing agents for this invention include cysteine, cysteamine, cystine, dimethylsulphoxide, methionine where the carboxyl group has been esterified, preferably by lower alkyl having 1 to 6 carbon atoms, e.g. methyl, S-methyl substituted ternary sulphonium derivatives of methionine such as methionine-S-methylsulphonium bromide, iodide or chloride. It will be noted that at least some of the above mentioned compounds have one or more optically active centres, in particular the aminoacids at the amino-and carboxyl-substituted carbon. To avoid doubt therefore, it is observed that the present invention extends to both individual isomers such as D- and L-isomers and enantiomers, and where two or more optically active centres are present, diastereoisomers, as well as mixtures of isomers including racemic DL-mixtures.

In accordance with the present invention, application onto the scalp of the synergistic composition of MSM with organic in vivo sulphydryl group releasing agents, improves its condition in terms of preventing hair loss and actually stimulating the growth of hair from those follicles whose function had been impaired or those which are blocked but not yet dead. Advantageously, a vasodilator such as for example menthol is included in order to further increase the effectiveness of the compositions within the scalp.

In another aspect, the present invention provides a composition of the present invention in intimate admixture with a physiologically acceptable carrier for use in improving the scalp condition through the combating of hair loss and baldness. This carrier is most preferably castor oil, which has been surprisingly found to significantly reduce excessive hair loss and even more surprisingly to react synergistically with the compositions of this invention.

In a further aspect, this submission provides a topical formulation comprising a combination of the invention in intimate admixture with a pharmaceutically acceptable vehicle. This vehicle should be acceptable in terms of being generally non-deleterious to the scalp of the subject being treated and compatible with the other ingredients of the formulation. It must be stressed that certain individuals have significantly more sensitive scalps than the average and it is therefore desirable that in these special cases alternative vehicles to those normally used, be employed.

Suitable vehicles are well known in the art, being noted for example in such standard works as the British National Formulary and the British Pharmacopoeia, and

include ointment bases and cream bases as well as lotions, pastes, jellies, sprays, aerosols and bath oils. Ointments and creams may contain oleaginois absorbtion colloidal clays, thickening agents such as gum tragacath or sodium alginate and other pharmaceutically acceptable accessory ingredients such as humectants, preservatives, buffers and antioxidants which have utility in such formulations.

The topical formulations of the invention contain at least 0.5%w/w of each of its ingredients, preferably from 1 to 30% w/w and most preferably form 1 to 10% w/w, e.g. 5% MSM and 2% dimethyl sulphoxide, cysteine or methylmethionine sulphonium chloride. When menthol is added, this is generally from 1 to 30% w/w and most preferably from 1 to 5% w/w.

In addition the compositions of this invention can be administered orally or parenterally in a suitable vehicle such as distilled waster but not castor oil.

For oral administration, the compositions of the invention and any accompanying material may be presented as a draught in water or in a syrup, in capsules, sachets, boluses or tablets, as an aqueous or oleaginous solution or suspension or in suspension in a syrup, such suspensions optionally including suspending agents or as an oil-in-water or water-in-oil emulsion. When desirable or necessary, flavouring, sweetening, preserving, thickening or emulsifying agents may be included in the formulation. Tablets may contain the compositions of the invention and any accompanying material as a powder or granules optionally mixed with binders, lubricants, inert diluents or surface active or dispersing agents.

For parenteral administration, the compositions of this invention and any accompanying material may be presented in sterile solutions or suspensions in aqueous or oleaginous vehicles, which may also contain preservatives, antioxidants and material for rendering the solution or suspension isotonic with the recipient's blood. Such formulations may conveniently be presented in unit-dose or multi-dose sealed containers.

For administration orally or parenterally, the active ingredients of this invention are preferably presented in solution, suspension, or emulsion at a concentration of from 0.5% to 15% w/v, more preferably 2 to 5% w/v in unit multidose form. When presented in unit dose form, each unit dose preferably contains from 50 to 500 mg of each of its ingredients. This dosage may be given one or more times daily, preferably at intervals of from 2 to 8 hours, most preferably every 6 hours. Advanteously, the ingredients of the invnetion are administered in a slow release or a sustained release vehicle, various suitable vehicles of this type being known in the art.

For topical therapy, the composition is applied onto the skin from 1 to 3 times a day whereby it is spread over the whole scalp and massaged in for about 3 to 5 minutes.

Further preferrred featues and advantages of the invention will be realized by way of the following examples which are being presented for illustration purposes only.

Example 1 - Preparation of Topical Formulations for Treating the Scalp

A.	Methyl sulphonylmethane	5g
	Dimethylsulphoxide	2g
	Cysteine hydrochloride	2g
	Menthol crystals	1g
	Castor oil	100ml
B.	Methyl sulphonylmethane	5g
	Dimethylsulphoxide	2g
	Methylmethionine sulphonium chloride	2g
	Menthol crystals	1g
	Castor oil	100ml
C.	Methyl sulphonylmethane	5g
	Dimethyl sulphoxide	2g
	Cysteine hydrochloride	2g
	Methylmethionine sulphonium chloride	2g
	Menthol crystals	1g
	Castor oil	100ml

These formulae are prepared at a temperature of around 25°c. Five grams of MSM are mixed with 2 grams of cysteine hydrochloride and/or methylmethionine sulphonium chloride in a glass container (stainless steel containers may also be used if large volumes are being prepared). Castor oil is then added and the contents stirred for a few minutes before being allowed to stand for 15 minutes. One gram of finely ground menthol crystals are then added. The mixture is left for another 15 minutes before 2 grams of dimethyl sulphoxide in solution form are added, the whole mixture is then stirred for a few minutes, and then left to stand for half an hour before being used. After

preparation, the formulations should not be left exposed to the air for long periods of time and should not be directly exposed to the sun. For storage, the product is placed in a dark-coloured airtight glass bottle and kept at an optimal temperature of 26°c away from direct sunlight.

Example 2 - Use of the Topical Treatment

The formulations mentioned above can be applied onto the scalp several times a day. An evening application may be left overnight then washed away the following morning with warm water and soap. It is most preferable that treatment be applied twice everyday with one application being left overnight. Treatment is usually extended for several months, most preferably eighteen months, whereby following an initial daily application for 6 months, treatment may be reduced to a single overnight application 3 times a week towards the end of the treatment course.

Example 3 - Detailed Evaluation of the Formulations

The following clinical trials were carried out on prospective randomized double blind basis. Randomization was effected by drawing sealed envelopes.

A. The effect of solutions of MSM, dimethylsuphoxide and MSM with dimethylsulphoxide prepared with double distilled water on excessive hair loss in men was examined. Treatment was topically applied onto the scalp alone twice daily and each application was massaged for a few minutes into the scalp. The evening dose was left overnight while the daytime dose was left on the scalp for 3 to 6 hours.

Patients were randomized into groups of twenty and the age range for the whole study was 25 to 39 years. . Treatment was carried out for four months then the treatment code was broken. The following observations were made:-

Treatment (n=20)	No further visible hair loss, n	%
0.5% MSM	1	5%
1% MSM	2	10%
2% MSM	3	15%
5% MSM	5	25%
10% MSM	5	25%
20% MSM	5	25%
30% MSM	5	25%
0.5% DMSO	1	5%
1% DMSO	1	5%
2% DMSO	2	10%
5% DMSO	2	10%
10% DMSO	2	10%
20% DMSO	2	10%
30% DMSO	2	10%
0.5% MSM+ 0.5% DMSO	4	20%
1% MSM + 1% DMSO	6	30%
2% MSM +2% DMSO	8	40%
5% MSM + 5% DMSO	12	60%
10% MSM + 10% DMSO	12	60%
20% MSM +20% DMSO	12	60%
30% MSM + 30% DMSO	12	60%

MSM: Methylsulphonylmethane

DMSO: Dimethylsulphoxide

In this study, excessive hair loss was defined as hair coming off while combing or massaging the scalp in addition to frequently being seen on the patient's clothes. Successful treatment meant that such hair fall was no longer seen. The results show that each of MSM and dimethyl sulphoxide exerted a benficial therapeutic effect regarding excessive hair loss, and that this action was synergistically heightened by their combination together. None of the therapeutic regimens produced allergies or adverse skin or systemic reactions and were all very well tolerated by the patients. This experiement shows that the doses of MSM and dimethyl sulphoxide listed in Example 1 are the most favourable (optimum dosage).

B. A further clinical trial was carried out employing the same protocol and addressing the same problem as the previous study, in order to examine the role of using more than one sulphydryl containing agent. The age range for the whole of this study was 24 to 36 years. The following observations were made:

Treatment (n=20)	No further visible hair loss, n	%
5% MSM + 2% DMSO	12	60%
2% cysteine hydrochloride	2	10%
5% MSM + 2% DMSO +2% cysteine hydrochloride	16	80%
2% methylmethionine sulphonium chloride	2	10%
5% MSM +2% DMSO + 2% methylmethionine sulphonium chloride	16	80%
2% cysteine hydrochloride + 2% methylmethionine sulphonium chloride	4	20%
5% MSM + 2% DMSO + 2% cysteine hydrochloride + 2% methylmethionine sulphonium chloride	20	100%

Solutions were prepared in double distilled water

MSM: Methylsulphonylmethane
DMSO: Dimethylsulphoxide

The results show that the addition of more than one sulphydryl-containing agent to MSM further enhances its therapeutic role against hair loss in a synergistic manner. No allergies or adverse local or systemic effects were encountered and all the regimens were well tolerated by the patients.

In this trial the doses of each of cysteine and methylmethionine sulphonium chloride were based on the experience obtained with dimethylsulphoxide in the previous trial.

C. A third trial was carried out to examine influences on the stimulation of hair growth which is defined as the actual and visible appearance of hair in a hitherto bald area. Patients were randomized into groups of twenty men (age range for the whole study was 28 to 43 years) then topically treated for 6 months with twice daily applications and leaving the evening application overnight. Therapy was then changed to twice a day, three times a week for a further 6 month period. Each application was gently massaged into the scalp for a few minutes. The day time dose was left on the scalp for at least 3 hours. All the formulations were prepared in accordance with the method detailed in Example 1. The treatment code was broken after one year of therapy. The following results were noted:-

Treatment (n=20)	Visible hair hair growth, n	%
Castor oil B.P.	0	0%
Castor oil + 1% menthol	2	10%
Castor oil + 1% menthol + 2% cysteine hydrochloride	4	20%
Castor oil + 1% menthol + 2% methylmethionine sulphonium chloride	4	20%
Castor oil + 1% menthol + 5% methylsulphonylmethane + 2% dimethyl sulphoxide	10	50%
Castor oil + 1% menthol + 5% methylsulphonylmethane + 2% dimethyl sulphoxide + 2% cysteine hydrochloride	14	70%
Castor oil + 1% menthol + 5% methylsulphonylmethane + 2% dimethyl sulphoxide + 2% methylmethionine sulphonium chloride	14	70%
Castor oil + 1% menthol + 5% methylsulphonylmethane + 2% dimethyl sulphoxide + 2% cysteine hydrochloride + 2% methylmethionine sulphonium chloride	18	90%

These results illustrate that addition of menthol to castor oil enhances the previoulsy known beneficial effects of the latter agent against hair loss and equips it with the power to stimulate hair growth to a significant degreee. Moreover, synergistic actions in the stimulation of hair growth were clearly achieved by the addition of an organic in vivo sulphydryl group releasing agent to the methylsulphonylmethane and dimethylsulphoxide combination. This trial further supports the efficacy of the preferred dosage levels of each of the active ingredients.

All the therapies employed were very well tolerated by all the patients and produced no allergies or any local or systemic adverse effects.

During this trial all the patients were physically examined every week and standard haematologial and biochemical tests (including liver and renal function tests, blood glucose, serum amylase and blood gases) with urine examination were also made at the same time. An electrocardiogram with cardiac enzymes' level estimation were performed every two weeks. No toxicity or biochemical/haematological abnormalities were detected in any case reflecting the safety of the formulations used.

It will be appreciated that although the methylsulponylmethane and sulphydryl group releasing agent are advantageously used in equal amounts, by weight, in the synergistic compositions of the invention, other ratios may also be used. Generally there is used a ratio of from 10:1 to 1:10, preferably from 5:1 to 1:5, most preferably about 1:1, by weight. It will be understood though that preferred proportions may differ from one amino acid to another and as noted hereinbefore preferred proportions of methylsulphonylmethane to cysteine or methionine are approximately 5:2 or 5:1.

CLAIMS

1. A synergistic composition, which composition comprises methylsulphonylmethane and a physiologically acceptable, organic, in vivo sulphydryl group releasing agent.

2. A composition as claimed in claim 1 wherein said sylphydryl group releasing agent is selected from cysteine, cysteamine, cystine, dimethylsulphoxide, methionine wherein the carboxyl group has been esterified, and S-methyl sustituted, ternary sulphonium, derivatives of methionine.

3. A composition as claimed in claim 2 wherein said carboxyl group has been esterified by lower alkyl having from 1 to 6 carbon atoms.

4. A composition as claimed in claim 2 wherein said methionine derivative comprises methionine-S-methyl sulphonium bromide, iodide or chloride.

5. A composition according to any one of claims 1 to 4 wherein said methylsulphonyl methane and sulphydryl group releasing agent are present in a ratio of from 1:5 to 5:1 by weight.

6. A composition according to any one of claims 1 to 5 which includes castor oil.

7. A composition according to any one of claims 1 to 6 which includes menthol.

8. A composition comprising methylsulphonylmethane and a physiologically acceptable, organic, in vivo sulphydryl group releasing agent for use in the

preparation of a formulation for at least one of arresting hair loss and stimulating hair growth.

9. A formulation comprising a composition according to any one of claims 1 to 7 in intimate admixture with a physiologically acceptable carrier therefor, for use in at least one of arresting hair loss and stimulating hair growth.

10. A formulation according to claim 9 wherein said carrier comprises castor oil.

11. A topical formulation according to claim 9 or 10 which contains at least 0.5% w/w of each of methylsulphonyl methane and the sulphydryl group releasing agent.

12. A formulation according to claim 11 which contains from 1 to 10% w/w of each of methylsulphonyl methane and the sulphydryl group releasing agent.

13. A topical formulation according to any one of claims 9 to 12 which includes from 1 to 30% w/w of menthol.

14. An oral formulation according to claim 10 which is in unit dosage form, each unit dose containing from 50 to 500 mg of each of methylsulphonylmethane and the sulphydryl group releasing agent.

15. A method of at least one of arresting hair loss and stimulating hair growth which comprises administering an effective dosage of a formulation according to claim 9.

16. A method according to claim 15 wherein is applied to the skin a topical formulation according to claim 11.

17. A method according to claim 16 wherein said topical formulation is applied to the scalp at least 2 times per day.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 057 875 (HERSCHLER R. J.) 8 April 1981 see claims see page 3, line 11 - line 26 see page 7; example 11	1,2,5
A	GB,A,2 057 263 (HERSCHLER R. J.) 1 April 1981 see claims	1-17
A	GB,A,2 177 917 (SALIM A. S. M.) 4 February 1987 see claims	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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